Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RAGAB EL-RASHIDY

Appeal No. 2002-0783
Application No. 09/268,957

ON BRIEF

WINTERS, SCHEINER, and LORIN, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal was taken from the examiner's decision rejecting claims 1 and 3 through 23, which are all of the claims remaining in the application.

The Invention

The invention relates to a controlled release composition containing sildenafil for delivery by the sublingual mode of administration. In addition to sildenafil, the composition includes an osmotic agent, a swellable hydrophilic carrier, and a water dispersible polymer. Claim 1, which is illustrative of the subject matter on appeal, reads as follows:

1. A composition providing a controlled release of sildenafil by sublingual route and consisting essentially of:

about 10 to about 75 milligrams of sildenafil;

an osmotic agent;

a swellable hydrophilic carrier; and

a water dispersible polymer;

the ratio of the amount by weight of the osmotic agent to the amount by weight of the swellable hydrophilic carrier being the range of about 0.3 to about 4; and

the composition having a T_{90} value in the range of more than about 25 to about 300.

The Prior Art References

The examiner relies on the following prior art references:

Bell et al. (Bell '534)	5,250,534	Oct. 5, 1993
Bell et al. (Bell '901)	5,346,901	Sep. 13, 1994
El-Rashidy et al. (El-Rashidy)	5,624,677	Apr. 29, 1997
Bell et al. (Bell '283)	5,719,283	Feb. 17, 1998

The Issue

The issue presented for review is whether the examiner erred in rejecting claims 1 and 3 through 23 under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of El-Rashidy and the above-cited Bell patents.

Deliberations

Our deliberations in this matter have included evaluation and review of the following materials: (1) the instant specification, including all of the claims on appeal; (2) applicant's Appeal Brief (Paper No. 10); (3) the Examiner's Answer (Paper No. 11); (4) the Reply Brief (Paper No. 12) excluding Exhibits A-E attached thereto; and (5) the above-cited prior art references.

On consideration of the record, including the above-listed materials, we affirm the examiner's rejection under 35 U.S.C. § 103(a).

Procedure

Applicant filed a Reply Brief received at the USPTO February 23, 2001 (Paper No. 12). As stated in 37 CFR § 1.193(b)(1), "The primary examiner must either acknowledge receipt and entry of the reply brief or withdraw the final rejection and reopen prosecution to respond to the reply brief." Here, the examiner did not withdraw the final rejection and reopen prosecution. It follows that the Reply Brief has been entered and made part of the administrative record (id.); this is consistent with the Office communication mailed May 7, 1991 (Paper No. 14), stating that the Reply Brief has been entered.

In his Reply Brief, applicant argues that the examiner's proposed combination of references is improper. Applicant relies on Exhibits A-E, attached to the Reply Brief, to support that argument. However, as stated in 37 CFR § 1.195, "Affidavits, declarations, or exhibits submitted afer the case has been appealed will not be admitted without a

showing of good and sufficient reasons why they were not earlier presented." In Paper No. 16, mailed February 13, 2003, the examiner determined that Exhibits A-E would not be admitted because applicant has not provided a showing of good and sufficient reasons why they were not earlier presented. Accordingly, those exhibits are not part of the administrative record.

In other words, applicant's Reply Brief is technically of record. But applicant's argument in the Reply Brief, with respect to the propriety of combining references, is unavailing because that argument is based on Exhibits A-E which are not of record. Cf., In re Mehta, 347 F.2d 859, 866, 146 USPQ 284, 289 (CCPA 1965) (Unsworn "Exhibit" can be taken merely as argument and not to establish facts).

The Merits

El-Rashidy discloses a composition comprising an osmotic agent; a swellable hydrophilic carrier; and a water dispersible polymer in combination with an effective amount of water soluble drug (active ingredient) for providing controlled release of the drug by sublingual route. Additionally, El-Rashidy discloses a T_{90} value and a ratio of the amount by weight of osmotic agent to the amount by weight of swellable hydrophilic carrier which meet the terms of claim 1 on appeal.

El-Rashidy discloses a composition for the controlled release of water soluble drugs by sublingual mode of administration, focusing attention on the specific drug apomorphine hydrochloride. As best seen in Example 19, El-Rashidy discloses apomorphine hydrochloride for treating male erectile dysfunction. According to El-

Rashidy,

> the apomorphine dose required to achieve a significant erectile response is usually accompanied by nausea or other serious undesirable side effects such as hypertension, flushing and diaphoresis. [El-Rashidy, Background of the Invention, column 2, lines 24-27]

and

> The present invention provides compositions that release water-soluble drugs relatively slowly over an extended time period. The composition is suitable for dosage forms that deliver drugs by the sublingual or buccal routes. In the practice of this invention with its application to the pharmacological agent, apomorphine, a sublingual tablet formulation that includes particular constituents permits the drug to achieve its effective therapeutic plasma concentration which is below a plasma concentration where undesirable side effects such as nausea and vomiting occur. In addition to this major improvement arising from the present invention, the added benefit of drug release over a longer period of time from the tablet can increase the duration of the therapeutic activity for the drug.
>
> The composition, in the form of a tablet, delivers the pharmacological agent, such as apomorphine, at a controlled rate to produce the desired physiological effect of the drug while preventing or diminishing the side effects such as hypotension, nausea and vomiting that have been associated with apomorphine. Such a composition thus provides the therapeutic benefits of apomorphine, as for example, in the treatment of Male Erectile Dysfunction . . . with minimal side effects. [El-Rashidy, Summary of the Invention, column 3, lines 17-40].

We agree with the examiner that it would have been well within the skill of the art and obvious to a person having ordinary skill to apply the teachings of El-Rashidy to the active ingredient sildenafil. In his specification, page 6, lines 15 and 16, applicant describes sildenafil as water soluble. Further, at the time the invention was made, the oral use of the citrate salt of sildenafil had been approved by the U.S. Food and Drug Administration (FDA) for treating male erectile dysfunction (specification, page 2, lines 30-33). In dose-response studies, increasing doses of sildenafil (25 to 100 mg)

reportedly increased the erectogenic efficacy of sildenafil (specification, page 3, lines 21-23). However, the oral administration of sildenafil is also accompanied by dose-responsive undesirable side effects. Consequently, at doses higher than 50 milligrams, the incidence of such side effects as abnormal vision problems ranging from blue or green halo effects to blurring, dyspepsia, nasal congestion, blinding headaches, flushing redness, diarrhea, dizziness, rash, and urinary tract infection increases (id., lines 23-31). Other more serious side effects have also been reported (specification, paragraph bridging pages 3 and 4). Thus, at the time the invention was made, there was a need and desire for oral administration forms that promote the bioavailability of sildenafil at lower doses while minimizing side effects (specification, page 4, lines 9-11).

Bell '534, Bell '901, and Bell '283 disclose that sildenafil and a suitable pharmaceutically acceptable vehicle or carrier may be prepared for sublingual administration. We are persuaded that a person having ordinary skill, armed with the disclosure of the Bell patents and the acknowledged state of the prior art described in applicant's specification, would have found it obvious to apply the teachings of El-Rashidy to the water soluble drug sildenafil. In this manner, a person having ordinary skill would have arrived at a composition providing a controlled release of sildenafil by sublingual route containing (1) from 25 to 100 milligrams of sildenafil; (2) an osmotic agent; (3) a swellable hydrophilic carrier; and (4) a water dispersible polymer. As disclosed by El-Rashidy, that composition would have a T_{90} value in the range of more than about 25 to about 300 and a ratio of the amount by weight percent of the osmotic agent to the amount by weight percent of the swellable hydrophilic carrier less than

about 4.

It is our judgment, therefore, that a person having ordinary skill would have arrived at the composition sought to be patented in claim 1 with a reasonable expectation of providing a rapid onset of action[1] and a controlled release of sildenafil; and promoting the bioavailability of sildenafil while minimizing adverse side effects. We therefore affirm the examiner's decision rejecting claim 1 under 35 U.S.C. § 103(a).

In Section D of his Appeal Brief, applicant emphasizes the amount of sildenafil recited in claims 3 through 22. Applicant argues that the cited references would not have suggested "from about 15 milligrams to about 50 milligrams of sildenafil" recited in dependent claim 3; or "about 10 to about 75 milligrams of sildenafil" recited in dependent claims 4 through 22.[2] Again, we find it sufficient to note that the oral use of the citrate salt of sildenafil had been approved by the U.S. Food and Drug Administration (FDA) for treating male erectile dysfunction at the time applicant's invention was made. (Specification, page 2, lines 30-33). In dose-response studies, increasing doses of sildenafil (25 to 100 mg) reportedly increased the erectogenic efficacy of sildenafil (Background of the Invention, applicant's specification, page 3, lines 21 through 23). In our judgment, therefore, the amount of sildenafil recited in

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[1] As pointed out in the Background of the Invention section of applicant's specification, page 4, lines 13-15, "[t]he main reason for sublingual route of drug administration is to provide a rapid onset of action of potent drugs."

[2] In independent claim 1, applicant recites a composition containing "about 10 to about 75 milligrams of sildenafil." Claims 4 through 22 depend from claim 1, "and then specify a further limitation of the subject matter claimed." 35 U.S.C. § 112, fourth paragraph. In each instance, that further limitation does not relate to or further restrict the amount of sildenafil.

claims 3 through 22 "reads on" an effective amount of this water soluble drug known in the art at the time the invention was made.

In section E of his Appeal Brief, applicant argues claim 23 separately. It is not entirely clear to us, however, what limitation in claim 23 applicant would rely on to patentably distinguish over the prior art. It may be that applicant would predicate patentability on the recitation "suitable for the treatment of psychogenic impotence" which appears in claim 23 but not claim 1. See the Appeal Brief, paragraph bridging pages 11 and 12 ("Here, even if the Bell et al. Patents are deemed to be properly combinable, arguendo, with the El-Rashidy et al. Patent, there is no indication whatsoever that out of the myriad of disclosed compounds one of ordinary skill would turn to sildenafil in the specific controlled release, sublingual composition for the successful treatment of psychogenic impotence" (emphasis added)). If this is so, the argument lacks merit. Again, at the time the invention was made, the oral use of the citrate salt of sildenafil had been approved by the U.S. Food and Drug Administration (FDA) for the treatment of male erectile dysfunction (Background of the Invention portion of applicant's specification, page 2, lines 30 through 33).

Conclusion

In conclusion, for reasons set forth in the body of this opinion, we affirm the rejection of claims 1 and 3 through 23 under 35 U.S.C. § 103(a) as unpatentable over the combined disclosures of El-Rashidy and the above-cited Bell patents.

The examiner's decision is affirmed.

No time period for taking any subsequent action in connection with this appeal

may be extended under 37 CFR § 1.136(a).

AFFIRMED

Sherman D. Winters Administrative Patent Judge	)
Toni R. Scheiner Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Hubert C. Lorin Administrative Patent Judge	)

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